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MESSAGE: Attached is a Reply Brief in response to Examiner's Answer dated November 5, 2003.

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CERTIFICATE OF TRANSMISSION BY FACSIMILE (37 CFR 1.8) Applicant(s): Anderson and Montelione			Docket No. RU-0075
Serial No. 09/181,601	Filing Date October 29, 1998	Examiner J. Fredman	Group Art Unit 1634

Invention: LINKING GENE SEQUENCE TO GENE FUNCTION BY THREE DIMENSIONAL (3D) PROTEIN STRUCTURE DETERMINATION

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	RU-0075
Inventors:	Anderson and Montelione
Serial No.:	09/181,601
Filing Date:	October 29, 1998
Examiner:	J. Fredman
Group Art Unit:	1634
Title:	Linking Gene Sequence to Gene Function by Three Dimensional (3D) Protein Structure Determination

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On December 30, 2003

Jane Massey Licata Registration No. 32,257

Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

REPLY BRIEF

This reply brief is being filed in response to the Examiner's Answer dated November 5, 2003 to address certain issues raised in the Examiner's Answer.

The claimed invention is a method for elucidating the function of proteins and protein domains by examination of their three dimensional structures, and more specifically by the use of bioinformatics, molecular biology and nuclear magnetic resonance spectroscopy to enable the rapid and automated determination of functions, as a means for genome analysis. In this method, a target polynucleotide which encodes a protein of unknown function is first parsed into at least one putative polypeptide domain. This parsing step is discussed at page 5, lines 23-25, page 7, lines 3-7 and lines 20-23, and page 10, lines 23-30 of the specification as filed. The second step of the instant method involves identifying a putative polypeptide domain consisting of 50 to 300 amino acids that properly folds into a stable polypeptide domain consisting of 50 to 300 amino acid residues. This identification step involving a domain of the claimed size range is taught at page 11, lines 29-34 of the specification as filed. In the third step of the claimed method, the three dimensional structure of the stable polypeptide domain is then determined. Methods for determining the three dimensional structure of the stable polypeptide domain are taught at pages 3-

5 and 9-10. The next step involves comparing the determined three dimensional structure of the stable polypeptide domain to known three dimensional structures in a protein data bank in order to identify known structures within the protein data bank that may be homologous to the determined three dimensional structure. This step in the method is discussed at page 24, lines 25-35. The final step in the claimed method involves correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain. This part of the method is described at page 25, lines 30-35 and page 26, lines 1-35. Further the method of the present invention is shown graphically as a flow chart in Figure 1.

Appellants respectfully disagree with several points of reasoning set forth by the Examiner as the basis for maintaining the rejection under 35 U.S.C. § 103 in the Answer dated November 5, 2003. Appellants believe that this reasoning fails to follow the basic tenets of an obviousness determination as set forth by both the Courts and MPEP § 2141.

(A) The claimed invention must be considered as a whole

Appellants do not believe that the claimed invention as whole has been considered. Specifically, at pages 11-13 of the Examiner's Answer, it is suggested that Wallace et al. teach the analysis of entire protein sequences which are of greater than 50 amino acids to determine the three amino acids involved in the

actual catalysis and that the three amino acids in the context of the folds and three dimensional structure and context provided by all the remaining amino acids in the protein must be considered.

However, the pending claims are expressly limited to protein domains of 50 to 300 amino acid residues. As is well-known in the art, a protein domain is a region within a protein that has been distinguished by a well-defined set of properties or characteristics. In general, a protein domain is less than the entire protein sequence and in the case of Wallace et al., the domain is comprised of three amino acids which are brought into close proximity by the entire protein structure. Thus, unlike Wallace et al., the instant invention relates to determining the function of proteins and protein domains by examining the three dimensional structure of structural domains wherein the entire protein sequence need not be utilized and the domains are 50 to 300 amino acids in length.

(B) The references must be considered as whole and must suggest the desirability and thus the obviousness of making the combination

Appellants disagree with the Examiner's reasoning at page 13 of the Examiner's Answer as well as the conclusion that it is clearly obvious in view of the prior art to employ protein domains of 50 to 300 amino acids in determining the function of unknown proteins.

The Examiner suggests that Holm et al. teach a comparison of the proper length of 50 to 300 amino acids in that the Adenovirus type 5 knob domain listed in table 1 at page 478 is 196 amino acids and that Holm et al. expressly note that the ordinary practitioner would want to perform a comparison, such as taught by Wallace et al., to determine the relationship of new proteins with proteins present in databases.

Wallace et al. teach and expressly demonstrate via the protein structures depicted in the figures that entire protein sequences were used in the determination of a catalytic triad domain consisting of three amino acids. Holm et al. provide one example of a sequence of 196 amino acids which was identified as a particular fold class or protein family. Nowhere in either Wallace et al. or Holm et al. do these references expressly teach or suggest the desirability of using structural domains of 50 to 300 amino acids in length for determining the three dimensional structure and function of unknown proteins. The fact that Holm et al. merely lists one protein amongst 20 that happens to be 196 amino acid in length is not motivation for one of skill in the art to identify a putative polypeptide domain consisting of 50 to 300 amino acids that properly folds into a stable polypeptide domain for use in determining three dimensional structure and subsequent function of an unknown protein.

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention

It also appears that hindsight vision afforded by the claimed invention may have been improperly used when interpreting prior art teachings referred to in the specification. For example, Appellants respectfully disagree with the Examiner's suggestion at page 15 of the Answer that significant motivation is provided to integrate the methods of Farber et al. and Wallace et al. in order to take unknown nucleic acid sequences and yield the result desired by Wallace et al. of identifying the function of the protein structure. As discussed in the main Appeal Brief, the general teaching of Farber et al. is of neural networks and information theory for determination of coding regions of DNA sequence. Nowhere is there any teaching or suggestion of the identification of protein domains of 50 to 300 amino acids for use in determining three dimensional structure and subsequent function of an unknown protein. Such broad implications as derived by the Examiner from this reference can only be done with the instant specification in hand.

(D) Reasonable expectation of success is the standard by which obviousness is determined

Finally, no reasonable expectation of success has been established for the claimed invention. Appellants strongly disagree with the Examiner's characterization at page 16 of the Answer that the express teachings of Wallace et al. and Holm et al. of how to perform the functional analysis of proteins by comparing the 3D structures and that 99.4% of the coding sequences will be parsed by the method of Farber et al. as evidence that these references provide reasonable expectation of success of the claimed invention.

One of skill cannot predict from the teachings of primary reference of Wallace et al. that a domain of 50 to 300 amino acids that properly folds into a stable polypeptide domain can be extracted from an unknown protein and be used in determining three dimensional structure and subsequent function of the unknown protein. First Wallace et al. teach the use of the entire protein sequence to determine the three amino acid domain which comprises the catalytic triad. Second, Wallace et al. then use the Ser-His-Asp catalytic triad domain template with an RMS distance cutoff of 2.0 Å to identify other proteins with triplets that lie within the constraints of this template. Thus, Wallace et al. do not teach success in using domains of 50 to 300 amino acids in determining the biochemical function of a protein or

polypeptide domain of unknown three dimensional structure and function.

The prior art, when viewed as whole, simply does not provide the requisite teaching or suggestion to render the claimed invention, when viewed as a whole, obvious.

Respectfully submitted,

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DATE: December 30, 2003

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